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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,570	02/19/2004	Nadine Carozzi	APA016US01	5780

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Bayer CropScience LP
Athenix Corporation
2 T.W. Alexander Drive
Research Triangle Park, NC 27709

EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	

NOTIFICATION DATE	DELIVERY MODE
12/06/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

blair.wilson@bayercropscience.com
destiny.davenport@bayercropscience.com
pamula.ramsey@bayercropscience.com

Office Action Summary	Application No.	Applicant(s)	
	10/782,570	CAROZZI ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,19,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,19,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The finality of the rejection of the Office action mailed 12 January 2010 is withdrawn.

2. Claims 1-11, 19 and 22-23 are pending.

3. The rejection of claims 1 and 4-7 under 35 U.S.C. 103(a) as being unpatentable over Ben-Dov et al (1996, Appl. Environ. Microbiol., 62:3140-3145) in view of Carlton et al (1985, Mol. Biol. Microb. Differ., Proc. Intl. Spore Conf., 9th, Meeting date 1984, pages 246-252; Ed. Hoch et al, Am.Soc. Microbiol., Washington, DC) and taken with the evidence of Applicant's response to the Request for Information under 37 CFR 1.105 is withdrawn in favor of the new rejection below.

4. The rejection of claims 2-3, 8-11, 19 and 22-23 under 35 U.S.C. 103(a) as being unpatentable over Ben-Dov et al in view of Carlton et al as applied to claims 1 and 4-7 above, and further in view of Koziel et al (1997, US Patent 5,625,136) is withdrawn in favor of the new rejection below.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1 and 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ben-Dov et al (1996, Appl. Environ. Microbiol., 62:3140-3145) in view of Liu et al (2000, US Patent 6,156,308) and further in view of Carlton et al (1985, Mol. Biol. Microb. Differ., Proc. Intl.

Spore Conf., 9th, Meeting date 1984, pages 246-252; Ed. Hoch et al, Am.Soc. Microbiol., Washington, DC) and further in view of deMaagd et al (2001, Trends. Genet. 17:193-199) and taken with the evidence of Applicant's response to the Request for Information under 37 CFR 1.105.

Applicant's response to the Request for Information under 37 CFR 1.105, filed 17 March 2009, indicate that the bacterial strain from which SEQ ID NO:1-4 were isolated is HD536, and available from the USDA.

The claims are drawn to a nucleic acid encoding a toxin comprising SEQ ID NO:2 or 4.

Ben-Dov et al teach restriction mapping of a *Bacillus thuringiensis* plasmid (pg 3141, left column, to pg 3143, right column, 3). The method involved isolating the plasmid DNA (pg 3140, right column, ¶4), cloning fragments in vectors that encode a selectable-marker protein heterologous to the endotoxin, and growing these clones were grown in an E. coli host cell (pg 3140, right column, ¶2; pg 3143, right column, ¶2); using the fragments in restriction mapping (pg 3141, left column, to pg 3143, right column, 3). Ben-Dov et al do not teach a nucleic acid encoding SEQ ID NO:2 or 4.

Liu et al teach that it would be advantageous to isolate new *B. thuringiensis* toxins to increase the spectrum of biopesticides (column 3, lines 6-8). Liu et al also teach a method of isolating *B. thuringiensis* toxin genes, involving sequencing the proteins from the toxin crystals, using them to make probes, using the probes to isolate the genes encoding the toxins, and sequencing the genes (column 15, line 19, to column 17, line 25). Liu et al also teach expressing the toxins in heterologous bacteria (column 6, line 25, to column 7, line 31).

Carlton et al teach that strain HD536 has a 68 MDa plasmid implicated in toxin production (Table 1).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to clone delta-endotoxin genes from strain HD536 described in Carlton et al using the methods described in Ben-Dov et al and Liu et al. One of ordinary skill in the art would have sequenced the plasmid fragments, translate the resulting sequences to identify open reading frames; comparison to known Cry protein conserved sequence and structural domains, as taught by deMaagd et al (paragraph spanning pg 193-194; Fig. 2) would aid indentifying Cry encoding reading frames. Further, use of probes made by the method Liu et al and designed from the protein sequences of toxins made by HD536 would have aided in cloning toxin genes, including those encoding SEQ ID NO:2 or 4, from that strain. The level of ordinary skill in this art is very high, as evidenced by each of Ben-Dov et al, Liu et al, and deMaagd et al.

One of ordinary skill in the art would have been motivated to do this cloning because an increased repertoire of delta-endotoxins would be desirable for increasing toxicity spectra, as taught by Liu et al (column 3, lines 6-8), and for overcoming pest resistance to existing endotoxins.

It is obvious to use the 68 MDa plasmid from HD536 because HD536 was known in the art as having a toxin-encoding plasmid (Carlton et al, Table 1). In cloning the toxins from the 68 MDa plasmid from HD536, one of skill in the art would necessarily isolate a nucleic acid encoding SEQ ID NO: 2 or 4.

It would be obvious to one of skill in the art to culture the host cell comprising the plasmid in conditions under which the nucleic acid encoding the toxins is expressed to study the

toxicity of the protein, particularly for toxicity to lepidopteran plant pests, and to produce large quantities of the toxin, as suggested by Liu et al (column 6, lines 25-36).

7. Claims 2-3, 8-11, 19 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ben-Dov et al in view of Carlton et al as applied to claims 1 and 4-7 above, and further in view of Koziel et al (1997, US Patent 5,625,136). The rejection is repeated for the reasons of record as set forth in the Office action mailed 15 July 2009, as applied to claims 2-3, 8-11, 19, 22-23, 25-26 and 28-29. Applicant did not argue this rejection separately from the previous one in the response filed 9 October 2009.

The claims are drawn to plants transformed with a nucleic acid encoding a toxin comprising SEQ ID NO:2 or 4, including plant optimized nucleic acids.

The teachings of Ben-Dov et al in view of Liu et al and further in view of Carlton et al and further in view of deMaagd et al are discussed above. Ben-Dov et al in view of Liu et al and further in view of Carlton et al and further in view of deMaagd et al do not teach plants and seeds transformed with the nucleic acid.

The teachings of Ben-Dov et al in view of Liu et al and further in view of Carlton et al and further in view of deMaagd et al are discussed above. Ben-Dov et al in view of Liu et al and further in view of Carlton et al and further in view of deMaagd et al do not teach plants and seeds transformed with the nucleic acid.

Koziel et al teach construction of a Cry endotoxin coding sequence that is designed for expression in a plant; this sequence has increased GC content relative to the native coding sequence (column 7, lines 19-56; column 9, lines 50-56). Koziel et al also teach expression of

the modified Cry endotoxin coding sequence in maize cells from a vector that also encodes phosphoenolpyrivate carboxylase (column 59, line 40, to column 63, line 50), as well as maize plants and seeds transformed with the modified Cry endotoxin coding sequence (claims 4-25).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to transform the nucleic acid made obvious by Ben-Dov et al in view of Liu et al and further in view of Carlton et al and further in view of deMaagd et al into plants, including maize, as described in Koziel et al. One of ordinary skill in the art would have been motivated to do so because the resultant plants will be more resistant to insect pests, and the farmer thus less likely to suffer economic loss because of them. Further, Lui et al also suggest expressing the toxins in plants (column 7, lines 32-38).

Response to Arguments

Applicant's arguments in the Appeal Brief filed 17 September 2010 to the rejection of over Ben-Dov et al in view of Carlton et al are addressed to the extent they apply to the new rejections.

Applicant urges outside of Applicant's specification one of ordinary skill in the art would have no reason to use HD536 given the numerous other strains having insecticidal activity (brief pg 4).

This is not found persuasive because Carlton et al teach that strain HD536 has a 68 MDa plasmid implicated in toxin production (Table 1). Carlton et al teach a finite number of such strains, 17. The motivation is using strain known to produce toxins rather ones not so known is

that one of skill in the art would know that cloning from a toxin-encoding strain would be successful.

Applicant urges Ben-Dov teach cloning large restriction fragments and using probe specific for known toxins (brief pg 4-5).

This is not found persuasive because Liu et al teach cloning and sequencing genes. One of ordinary skill in the art would have sequenced the plasmid fragments, translate the resulting sequences to identify open reading frames; comparison to known Cry protein conserved sequence and structural domains would aid indentifying Cry encoding reading frames taught by deMaagd et al.

Applicant urges Carlton fail to make up for the deficiencies of Ben-Dov et al (brief pg 5).

This is not found persuasive because Liu et al teach cloning and sequencing genes. One of ordinary skill in the art would have sequenced the plasmid fragments, translate the resulting sequences to identify open reading frames; comparison to known Cry protein conserved sequence and structural domains would aid indentifying Cry encoding reading frames taught by deMaagd et al.

Applicant urges one of ordinary skill in the art would have no motivation to combine Ben-Dov and Carlton et al; Ben-Dov uses probes that hybridize to mosquito toxins, and there is no motivation to apply this methodology to other toxins (brief pg 5-6).

This is not found persuasive. The level of ordinary skill in this art is very high, as evidenced by each of Ben-Dov et al, Liu et al, and deMaagd et al. Use of Ben-Dov's probes would not be necessary, as Liu et al teach making probes designed from the protein sequences of toxins encoded by a bacterial strain. The motivation to apply this methodology to other toxins

comes from a desire to have an increased repertoire of delta-endotoxins for increasing toxicity spectra, as taught by Liu et al (column 3, lines 6-8), and for overcoming pest resistance to existing endotoxins.

Applicant urges an obvious to try rationale requires that there by a finite number of possibilities; further no insecticidal activity was demonstrated for this strain prior to Applicant's disclosure (brief pg 6).

This is not found persuasive Carlton et al teach that strain HD536 has a 68 MDa plasmid implicated in toxin production. This is one of only 17 strains Carlton teaches. Applicant has provided no support for their assertion that no insecticidal activity was demonstrated for this strain prior to their disclosure; such support of required given Carlton's teaching of toxin production from this strain.

Applicant urges one of skill in the art would have no motivation to use Ben-Dov's probes; the claimed sequences have low sequence homology to other known toxins, including the probes used by Ben-Dov (brief pg 6-7).

This is not found persuasive. Use of Ben-Dov's probes would not be necessary, as Liu et al teach making probes designed from the protein sequences of toxins encoded by a bacterial strain. The motivation to apply this methodology to other toxins comes from a desire to have an increased repertoire of delta-endotoxins for increasing toxicity spectra, as taught by Liu et al (column 3, lines 6-8), and for overcoming pest resistance to existing endotoxins.

Applicant urges one of ordinary skill in the art would have no motivation to isolate SEQ ID NO:1-4 from HD536 of Carlton et al; HD536 is only one strain in a list and Carlton et al

does not specifically indicate why it would be advantageous to isolate sequences from this strain (brief pg 7-8).

This is not found persuasive. Carlton teaches a mere 17 strains that produce toxins; this far fewer than the 53 pharmaceutically acceptable salts found to be a finite number in *Pfizer Inc. v. Apotex Inc.,* 82 USPQ2d 1852 (Fed. Cir. 2007). It would advantageous to isolate sequences from this strain because it was known in the art to produce toxins.

KSR International Co. v. Teleflex Inc., for the proposition that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." 127 S. Ct. 1727, 1732, 82 USPQ 2d 1385, 1397 (2007).

It is noted that Applicant only cloned SEQ ID NO:1-4 from HD536. SEQ ID NO:5 and 6 are sequences of prior art endotoxins cry1Aa and cry1Ac (legend to Fig 1).

Applicant urges in Eisai there was no reason to make the substitution because there was no reason to make the particular modifications claimed to the lead compound (brief pg 7-8).

This is not found persuasive. The case is not analogous, as no modifications were made to any compound. The HD536 68 kDa plasmid is necessary to achieve the claimed molecule; all that is required is sequencing the plasmid. As discussed above, there Carlton taught a finite number of toxin-producing strains; the need for additional toxins provided the motivation to isolate the toxins-encoding genes from those strains.

Applicant urges AXMI-007 unexpectedly exhibits insecticidal activity against *Lygus lineolaris* (brief pg 8).

This is not found persuasive. Applicant has not shown that the toxin provides activity previously shown not to be present in HD536 or present on the 68 kDa plasmid. There is no teaching, for example, that HD536 was not toxic to *L. lineolaris*. Thus, this activity cannot be unexpected. It is unclear why the low homology AXMI-007 to other toxins would make toxicity to *L. lineolaris* unpredictable.

Applicant's arguments in the Appeal Brief filed 17 September 2010 to the rejection of over Ben-Dov et al in view of Carlton et al and further in view of Koziel et al are addressed to the extent they apply to the new rejections.

Applicant urges there is no motivation to transform the nucleic acids into plant or cells; Ben-Dov has no association with plants, as they were concerned with mosquito toxins and motivation is not found in Carlton (brief pg 9).

This is not found persuasive. The level of ordinary skill in this art is very high, as evidenced by each of Ben-Dov et al, Liu et al, and deMaagd et al. Use of Ben-Dov's probes would not be necessary, as Liu et al teach making probes designed from the protein sequences of toxins encoded by a bacterial strain. The motivation to apply this methodology to other toxins comes from a desire to have an increased repertoire of delta-endotoxins for increasing toxicity spectra, as taught by Liu et al (column 3, lines 6-8), and for overcoming pest resistance to existing endotoxins.

Conclusion

8. No claim is allowed

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, Ph.D., whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

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December 1, 2010

/Anne R Kubelik/
Primary Examiner, Art Unit 1638

/Anne Marie Grunberg/

Supervisory Patent Examiner, Art Unit 1638